

Impaired Coronary Blood Flow in Nonculprit Arteries in the Setting of Acute Myocardial Infarction

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OBJECTIVES AND BACKGROUND	While attention has focused on coronary blood flow in the culprit artery in acute myocardial infarction (MI), flow in the nonculprit artery has not been studied widely, in part because it has been assumed to be normal. We hypothesized that slower flow in culprit arteries, larger territories infarcted and hemodynamic perturbations may be associated with slow flow in nonculprit arteries.
METHODS	The number of frames for dye to first reach distal landmarks (corrected TIMI [Thrombolysis in Acute Myocardial Infarction] frame count [CTFC]) were counted in 1,817 nonculprit arteries from the TIMI 4, 10A, 10B and 14 thrombolytic trials.
RESULTS	Nonculprit artery flow was slowed to 30.9 ± 15.0 frames at 90 min after thrombolytic administration, which is 45% slower than normal flow in the absence of acute MI (21 ± 3.1 , $p < 0.0001$). Patients with TIMI grade 3 flow in the culprit artery had faster nonculprit artery CTFCs than those patients with TIMI grades 0, 1 or 2 flow (29.1 ± 13.7 , $n = 1,050$ vs. 33.3 ± 16.1 , $n = 752$, $p < 0.0001$). The nonculprit artery CTFC improved between 60 and 90 min (3.3 ± 17.9 frames, $n = 432$, $p = 0.0001$), and improvements were related to improved culprit artery flow ($p = 0.0005$). Correlates of slower nonculprit artery flow included a pulsatile flow pattern (i.e., systolic flow reversal) in the nonculprit artery ($p < 0.0001$) and in the culprit artery ($p = 0.01$), a left anterior descending artery culprit artery location ($p < 0.0001$), a decreased systolic blood pressure ($p = 0.01$), a decreased ventriculographic cardiac output ($p = 0.02$), a decreased double product ($p = 0.0002$), a greater percent diameter stenosis of the nonculprit artery ($p = 0.01$) and a greater percent of the culprit artery bed lying distal to the stenosis ($p = 0.04$). Adjunctive percutaneous transluminal coronary angioplasty (PTCA) of the culprit artery restored a culprit artery CTFC (30.4 ± 22.2) that was similar to that in the nonculprit artery at 90 min (30.2 ± 13.5), but both were slower than normal CTFCs (21 ± 3.1 , $p < 0.0005$ for both). If flow in the nonculprit artery was abnormal (CTFC ≥ 28 frames) then the CTFC after PTCA in the culprit artery was 17% slower ($p = 0.01$). Patients who died had slower global CTFCs (mean CTFC for the three arteries) than patients who survived (46.8 ± 21.3 , $n = 47$ vs. 39.4 ± 16.7 , $n = 1,055$, $p = 0.02$).
CONCLUSIONS	Acute MI slows flow globally, and slower global flow is associated with adverse outcomes. Relief of the culprit artery stenosis by PTCA restored culprit artery flow to that in the nonculprit artery, but both were 45% slower than normal flow. (J Am Coll Cardiol 1999;34: 974–82) © 1999 by the American College of Cardiology

The thrombolysis in acute myocardial infarction (TIMI) flow grade (1) in the culprit artery has been the focus of angiographic trials in patients with acute myocardial infarction (MI) (2–7). It has been assumed that flow in nonculprit

arteries is normal (1), and little or no attention has been paid to global measures of flow in all three coronary arteries. Recently, we described a new index of coronary blood flow, the corrected TIMI frame count (CTFC), in which the number of frames required for contrast material to reach standardized distal landmarks is counted (8). In our initial description of the CTFC, we noted, in a relatively small number of patients ($n = 77$), that flow was slowed in nonculprit arteries compared with patients with normal flow in the absence of acute MI (25.5 ± 9.8 vs. 21 ± 3.1 , $p =$

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Abbreviations and Acronyms

ANOVA	= analysis of variance
CHF	= congestive heart failure
CTFC	= corrected TIMI frame count
EF	= ejection fraction
LAD	= left anterior descending artery
LCx	= left circumflex artery
MI	= myocardial infarction
MRI	= magnetic resonance imaging
PTCA	= percutaneous transluminal coronary angioplasty
RCA	= right coronary artery
rt-PA	= recombinant tissue plasminogen activator
TIMI	= Thrombolysis in Acute Myocardial Infarction
tPA	= tissue plasminogen activator

0.0001) (8). The goal of the present study was to validate prospectively this observation in a large number of patients, and to examine the determinants of slowed flow in nonculprit arteries. We hypothesized that there would be an association between flows in culprit and nonculprit arteries, and in their improvement over time. We also hypothesized that slow flow would be related to hemodynamic perturbations in the setting of acute MI, and prospectively collected hemodynamic data to examine this hypothesis. This study also examines the relationship between an index of global flow (the average frame count of all three arteries) to clinical outcomes.

METHODS

The data are drawn from four TIMI trials: TIMI 4, 10A, 10B and 14. The TIMI 4 trial was a randomized double-blind comparison of three thrombolytic regimens in 416 patients (9): Anistreplase (Eminase or APSAC) versus front-loaded recombinant tissue plasminogen activator (rt-PA) (Activase or alteplase) versus combination therapy. The TIMI 10A trial was a nonrandomized, open-label, dose escalation study of eight ascending doses of TNK (5, 7.5, 10, 15, 20, 30, 40, 50 mg IV over 5 to 10 s) in 113 patients (10). TIMI 10B was a randomized trial of 30-, 40- and 50-mg doses of TNK versus front-loaded rt-PA in 853 patients. There were 812 patients available for analysis from the ongoing TIMI 14 trial comparing abciximab versus abciximab plus low-dose thrombolytic (either tissue plasminogen activator [tPA] or streptokinase). Angiography was performed at 60, 75 and 90 min after thrombolysis (8–10). Nitroglycerin (IV or sublingual) was administered every 15 min if the systolic blood pressure exceeded 110 mm Hg (8–10). Hemodynamic data were collected prospectively in the TIMI 14 trial. Adverse outcomes were adjudicated by clinical events committees. The TIMI studies were approved by each participating center's Institutional Review Board, and the trial was conducted according to the principles of the Declaration of Helsinki.

Angiographic analysis methods. Culprit artery location was based upon the qualifying electrocardiogram, the presence of a thrombotic or ulcerated lesion and the presence of a wall motion abnormality on left ventriculography, when available. The TIMI flow grade was assessed at the TIMI Angiographic Core Laboratory as previously defined (1). To evaluate objectively coronary flow as a continuous variable, the number of cineframes required for contrast to reach standardized distal coronary landmarks (the TIMI frame count) was measured using a frame counter on a cineviewer and converted to the U.S. standard of 30 frames/s (8,11). Flow was defined to be abnormal when the CTFC was ≥ 28 frames (i.e., outside the 95% confidence interval for flow in patients without acute MI) (8). Pulsatile flow was defined as cessation of antegrade contrast motion or frank reversal of contrast motion during systole. End-diastolic frames of views that minimized foreshortening were chosen for quantitative coronary arteriography of the culprit lesion using a previously described and validated automated edge detection algorithm (12). Nonculprit lesions were analyzed using digital calipers (13–15). Wall motion abnormality was assessed in each region of the heart: anterobasal, anterolateral, apical, inferior and posterobasal. Each wall segment was classified as either normal, hypokinetic, akinetic or dyskinetic. Post-assessment, the non-infarct-related artery was matched with the corresponding wall region to determine wall motion abnormality. In left anterior descending artery (LAD) nonculprit arteries, the corresponding wall regions for determining abnormality were the anterobasal, anterolateral and apical regions. In left circumflex nonculprit arteries, the corresponding wall regions for determining abnormality were the anterolateral and inferior regions. In right coronary artery (RCA) nonculprit arteries, the corresponding wall regions for determining abnormality were the posterobasal and inferior regions.

Statistical analysis. All analyses were performed using Stata Statistical Software (Stata Corp., College Station, Texas). All continuous variable values are reported as the mean \pm SD. The Student *t* test and analysis of variance (ANOVA) with a Bonferroni correction were used in the analysis of normally distributed continuous variables. A Wilcoxon rank-sum test was used for variables that were not normally distributed. Chi-square tests were used to assess categorical variables when appropriate. A *p* value of <0.10 was required for retention in multiple linear and multiple logistic regression models. Patients were randomized into two random cohorts, and the univariate and multivariate correlates were validated independently in the two cohorts.

RESULTS

Baseline characteristics can be found in Table 1. The CTFC for nonculprit arteries at 90 min after thrombolytic administration was unimodally distributed with a single peak and a long tail, similar to previously published data for the CTFC in culprit arteries (Fig. 1) (8).

Table 1. Baseline Characteristics of Patients with Noninfarct-related Artery

Characteristic	
Age (years)	60.1 ± 11.9 (n = 612)
Gender (% male)	77.1% (n = 471/611)
Height (cm)	171.3 (n = 542)
Weight (kg)	79.7 (n = 543)
Race (% white)	73.4% (n = 448/610)
History of myocardial infarction	14.0% (n = 85/607)
Smoker at admission (%)	46.0% (n = 280/609)
History of congestive heart failure (%)	2.8% (n = 16/563)
History of hypertension (%)	37.7% (n = 226/600)
History of diabetes (%)	14.1% (n = 85/604)
Systolic blood pressure (mm Hg)*	134.9 ± 21.9 (n = 610)
Diastolic blood pressure (mm Hg)*	79.8 ± 14.8 (n = 606)
Pulse (beats/min)*	77.1 ± 17.5 (n = 609)

* Blood pressure and pulse on admission were available in TIMI 4, 10A and 10B. Blood pressure and pulse in TIMI 14 were at the 90-min catheterization, and are not included in this table.

Relation between culprit and nonculprit flow at 90 min after thrombolysis. In the TIMI 10A, 10B and 14 trials, the CTFC in nonculprit arteries was elevated to 31.1 ± 15.1 (n = 1,740, $p < 0.0001$ vs. normal flow), prospectively validating the results initially observed in TIMI 4 (8). Taking all trials together, nonculprit artery flow was slowed to 30.9 ± 15 frames at 90 min (n = 1,817), which is 45% slower than the normal value of 21 ± 3.1 (n = 78) reported for flow in the absence of acute MI ($p < 0.0001$) (8). Nonculprit CTFCs were slower than culprit CTFCs in 27% of patients (n = 387/1,441) whose nonculprit arteries had

lesions $<50\%$ diameter stenosis. We prospectively validated the benchmark of 21 frames by assessing the CTFC in the absence of acute coronary syndromes and found the CTFC to be 21.3 ± 6 (n = 102). Taken together, in all arteries with normal flow in the absence of acute MI, the normal CTFC was 21.2 ± 4.9 (n = 180).

Slower culprit artery flow was associated with slower nonculprit artery flow ($r = 0.24$, $p < 0.0001$), and culprit arteries that did not achieve TIMI 3 flow or a normal CTFC (<28 frames) had slower nonculprit artery flow ($p < 0.0001$) (Tables 2 and 3). When the LAD was the culprit artery, flow in the nonculprit artery was significantly slower than when either the left circumflex artery (LCx) or the RCA were the culprit artery ($p < 0.0001$) (Fig. 2). Pulsatile flow in the culprit artery was associated with an increased incidence of pulsatile flow in nonculprit arteries ($p < 0.001$), as well as slower nonculprit flow ($p = 0.01$) (Table 4). A greater reference diameter of the culprit artery ($p < 0.0001$) and a greater percent of the culprit artery bed (i.e., length of all distal branches <1.5 mm in diameter) lying distal to the culprit stenosis ($p = 0.04$) were both associated with slower nonculprit artery flow (Table 3).

Nonculprit artery predictors of nonculprit artery flow.

The presence of an obstructive lesion $>50\%$ by visual estimation in the nonculprit artery did not significantly impact the CTFC (30.5 ± 14.2 , n = 1,165 without lesion vs. 31.8 ± 16.4 ; n = 633 with at least one lesion, $p = \text{NS}$). In an analysis confined to nonculprit arteries with an obstructive lesion $>50\%$ by visual estimation, tighter nonculprit artery minimum lumen diameters and percent diameter stenoses were associated with slower nonculprit artery flow (Table 3, $p = 0.01$). Nonculprit artery flow was slower when the nonculprit artery had a pulsatile flow pattern ($p <$

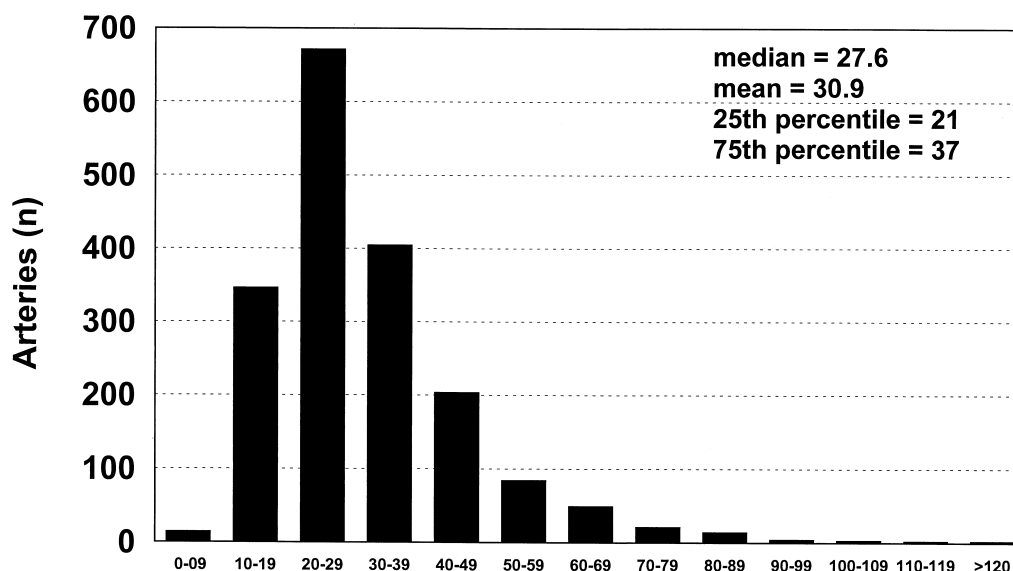


Figure 1. Distribution of the CTFC in nonculprit arteries at 90 min after thrombolytic administration. Nonculprit CTFC was unimodally distributed with a single peak and a long tail, similar to previously published data for the CTFC in culprit arteries (8).

Table 2. Univariate Predictors of Nonculprit 90-min Flow (CTFC): Categorical Variables*

	Present	Absent	p Value
Abnormal flow (CTFC ≥ 28) in culprit artery	33.5 \pm 16.1 (n = 844)	27.8 \pm 13.0 (n = 600)	< 0.0001
TIMI grade 3 flow in culprit at 60 min	28.9 \pm 13.4 (n = 335)	34.0 \pm 16.5 (n = 412)	< 0.0001
TIMI grade 3 flow in culprit at 75 min	28.6 \pm 13.0 (n = 476)	34.1 \pm 16.2 (n = 444)	< 0.0001
TIMI grade 3 flow in culprit at 90 min	29.1 \pm 13.7 (n = 1,050)	33.3 \pm 16.1 (n = 752)	< 0.0001
Culprit left anterior descending artery location	32.8 \pm 15.4 (n = 820)	29.3 \pm 14.5 (n = 997)	< 0.0001
Culprit location ipsilateral to nonculprit location	32.2 \pm 14.3 (n = 796)	29.8 \pm 15.4 (n = 1,018)	< 0.0001
Culprit receives collaterals from nonculprit artery	28.5 \pm 14.6 (n = 280)	31.5 \pm 15.0 (n = 1,442)	0.0001
Pulsatile flow in nonculprit artery	36.8 \pm 16.2 (n = 248)	30.2 \pm 14.9 (n = 1,333)	< 0.0001

* Nonculprit CTFCs were ascertained at 90 min after thrombolysis. The following variables were validated as associated with the nonculprit CTFC in two separate random cohorts: abnormal flow in culprit (p < 0.0001 for both); grade 3 flow in culprit at 60 min (p < 0.0001 and p = 0.02); grade 3 flow in culprit at 75 min (p < 0.0001 and p = 0.001); grade 3 flow in culprit at 90 min (p < 0.0001 for both); culprit LAD location (p < 0.0001 and p = 0.001); and pulsatile flow in the nonculprit artery (p < 0.0001). There was a trend towards validation for culprit arteries receiving collaterals from nonculprit arteries (p = 0.0004 and p = 0.07).

CTFC = corrected TIMI frame count.

0.0001 in two cohorts), and when the culprit artery was not collateralized (p = 0.01) (Table 2).

Hemodynamic correlates of nonculprit artery flow. Hemodynamic data were collected and analyzed prospectively in the TIMI 14 trial. Lower systolic (p = 0.01, n = 339), mean arterial blood pressures (p = 0.04, n = 248) and heart rates (p = 0.04, n = 280) were associated with slower nonculprit artery flow. In 90 patients, a reduced ventriculographic cardiac output (calculated by multiplying heart rate and stroke volume) was associated with slower nonculprit artery flow (p = 0.02), as was a decreased pressure-rate product (calculated by multiplying systolic blood pressure and heart rate, p = 0.0002, n = 268) and a narrower pulse pressure (p = 0.001, n = 338) (Table 3). Neither the pulmonary capillary wedge pressure nor the left ventricular end diastolic pressure achieved statistical significance.

Wall motion abnormalities within the distribution of the nonculprit artery. Patients with abnormal nonculprit artery flow (i.e., a CTFC ≥ 28) had a higher incidence of regional wall motion abnormalities within the distribution of the nonculprit artery (p < 0.001, Fig. 3). Likewise, when

the analysis was restricted to patients without a prior MI, similar findings were observed (p = 0.038).

Changes in nonculprit artery CTFC over time. In both unpaired and paired analyses, flow in nonculprit arteries improved between 60 and 90 min after thrombolysis (Fig. 4). There were greater improvements in nonculprit artery flow when the culprit artery flow also improved (7.4 vs. 1.0 frames, p < 0.0001; Fig. 5).

Relationship between the 90-min CTFC in nonculprit arteries and the culprit artery CTFC after angioplasty. Slower flow in the culprit artery after relief of the residual stenosis by adjunctive angioplasty was associated with slower 90-min nonculprit artery flow (p = 0.02). Indeed, post-percutaneous transluminal coronary angioplasty (PTCA) flow was 17% slower if the associated nonculprit artery flow was abnormal at 90 min (i.e., ≥ 28 frames) (32.8 \pm 21.8 vs. 28 \pm 22.4, p = 0.01). In a paired analysis, PTCA of the residual stenosis in the culprit artery restored a CTFC that was similar to that in the nonculprit artery at 90 min in a paired analysis (30.4 \pm 22.2 vs. 30.2 \pm 13.5,

Table 3. Univariate Predictors of Nonculprit 90-min Flow (CTFC): Continuous Variables*

	Number of Observations	t Statistic	Correlation Coefficient	p Value
Culprit CTFC (frames)	1,444	8.2	0.21	< 0.0001
Culprit reference diameter (mm)	1,767	4.4	0.10	< 0.0001
Systolic blood pressure (mm Hg)	339	-2.5	0.13	0.01
Mean arterial blood pressure (mm Hg)	248	-2.1	0.13	0.04
Ventriculographic cardiac output (liters/min)	90	-2.3	0.24	0.02
Double product	269	-3.8	0.22	0.0002
Percent of culprit artery bed distal to stenosis (including branches) (%)	49	2.1	0.29	0.04
Nonculprit minimum lumen diameter (mm)	223	-2.6	0.17	0.01
Nonculprit percent diameter stenosis (%)	223	2.6	0.17	0.01

* All variables were ascertained at 90 min after thrombolysis. The following variables were validated as associated with nonculprit CTFC in two separate random cohorts: culprit CTFC (p < 0.0001 in both cohorts); culprit reference diameter (p < 0.0001 and p = 0.015); double product (p = 0.01 and p = 0.006); and nonculprit minimum lumen diameter (p < 0.0001 in both cohorts). There was a tendency for the following variables to be valid in two separate random cohorts: systolic blood pressure (p = 0.04 and p = 0.152); and nonculprit percent diameter stenosis (p = 0.04 and p = 0.146).

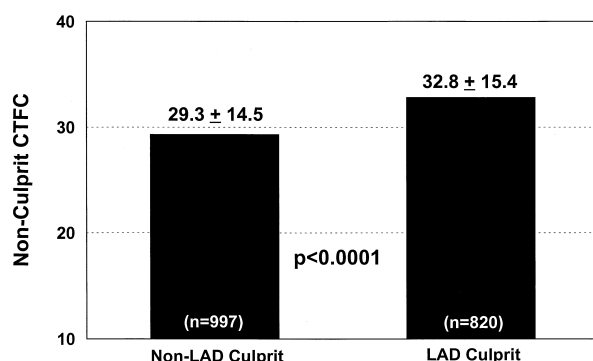


Figure 2. Relationship between culprit artery flow and nonculprit artery flow for the LAD versus other locations. If the LAD was the culprit artery, then nonculprit artery flow was slower by approximately 3.5 frames.

n = 254), but both were slower than normal (21 ± 3.1 frames, $p < 0.0005$ for both).

Multivariable model for the 90-min CTFC in nonculprit arteries. In a multivariate analysis, slower nonculprit artery CTFCs were associated independently with slower culprit artery CTFCs ($p < 0.001$), LAD culprit artery location ($p < 0.001$), larger culprit artery reference segment diameters ($p = 0.001$) and a pulsatile flow pattern in the nonculprit artery ($p < 0.001$). All variables remained independent predictors when validated in two separate cohorts. In a multivariable model restricted to arteries with hemodynamic data available (n = 226), slower nonculprit artery flow was associated with a slower heart rate ($p = 0.002$) and a lower systolic blood pressure ($p = 0.002$). When heart rate and blood pressure were removed from the model (which are used to calculate cardiac output and double product), it was also associated with reduced ventriculographic cardiac output ($p = 0.05$) and a decreased double product ($p = 0.003$) in a multivariate model (n = 89).

Role of hemodynamic perturbations in explaining slow nonculprit artery flow in acute MI. To gain insight as to whether perturbations in hemodynamics explained all of the abnormalities in nonculprit artery flows, the CTFC in patients with and without acute MI were compared in a multivariable model that included both acute MI and normal patients' (n = 102) hemodynamic data. In a multivariate analysis correcting for heart rate, systolic and dia-

stolic blood pressures, the nonculprit artery CTFC in the setting of acute MI still remained 11.7 frames slower than that in the absence of acute MI ($p = 0.0004$).

Relationship between flow in all three arteries and clinical outcomes. Given that flow was slowed globally, the average CTFC of all three epicardial arteries at 90 min after thrombolysis (the global CTFC) was analyzed to determine if there was a relationship to adverse outcomes (a composite adverse end point of in-hospital death, recurrent MI, new shock or severe congestive heart failure [CHF], or an ejection fraction [EF] <40%) (Fig. 6). Patients who remained event free had faster global CTFCs than patients who experienced an adverse outcome ($p = 0.005$). Likewise, when the analysis was restricted to patients without a prior MI, global CTFCs were faster in event-free patients than in those who had an adverse outcome ($p = 0.009$). When the end points were examined individually, global flow was slower in those patients who died ($p = 0.02$), in those with an EF <40% ($p = 0.02$) and in those with shock ($p = 0.03$). It tended to be slower in patients with death or recurrent MI ($p = 0.054$). Similar trends were seen when the analysis was restricted to patients without a prior MI ($p = 0.06$ for death, $p = 0.07$ for EF <40%, $p = 0.01$ for shock, $p = 0.05$ for death or recurrent MI).

DISCUSSION

Relief of the coronary obstruction by thrombolysis or percutaneous catheter-based intervention and restoration of normal flow in the culprit artery has been the goal of therapy in patients with acute MI. This analysis shows, however, that acute MI slows flow not only in the culprit artery, but also in the nonculprit artery by 45%. Culprit and nonculprit artery flows were linked, and relief of the residual stenosis in the culprit artery restored flow to the culprit artery, which was the same as in the nonculprit arteries (both 30 frames). Although improved post-PTCA, both culprit and nonculprit artery flows were still 45% slower than normal (21 frames). Multiple variables were associated with slower nonculprit artery flow: slower flow in the associated culprit artery, a larger territory infarcted (e.g., larger diameter culprit arteries with a larger percent of the culprit vessel distal to the stenosis, the absence of collaterals, LAD as the culprit artery), tighter stenoses within the nonculprit artery, the closer proximity or the ipsilateral location of the culprit

Table 4. Relationship Between Pulsatile Flow in Culprit Artery and Flow in Nonculprit Artery

	Culprit With Continuous Flow Pattern	Culprit With Pulsatile Flow Pattern	p Value
Percent of nonculprit arteries with pulsatile flow (%)†	13.2% (354/2,683)	26.6% (87/327)	< 0.001
CTFC of nonculprit arteries (frames)	30.9 ± 15.0 (n = 1,390)	33.5 ± 15.9 (n = 190)	0.01

*All variables were ascertained at 90 min after thrombolysis. †The association was validated in two random cohorts of patients: $p < 0.001$ for both data sets.

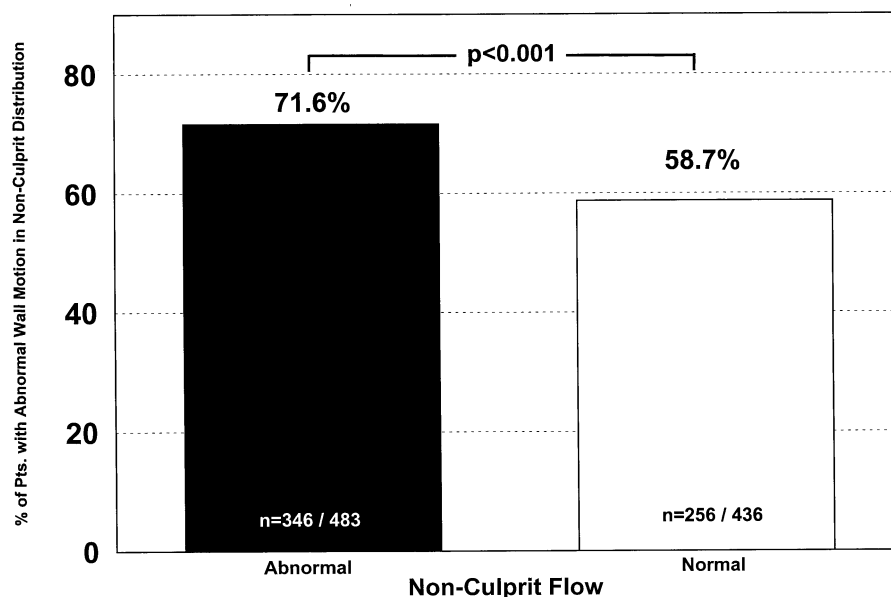


Figure 3. Relationship between the presence of abnormal flow (CTFC ≥ 28) in nonculprit arteries and a wall motion abnormality within the distribution of the nonculprit artery. Patients with abnormal nonculprit artery flow had a greater frequency of regional wall motion abnormalities within the distribution of the nonculprit artery ($p < 0.001$). When the analysis was restricted to patients without a prior MI, similar findings were observed ($p = 0.038$).

artery, lower systolic blood pressure, lower cardiac output and a lower double product (an index of oxygen consumption). Thus, acute MI slows flow globally, and this study shows that slower global flow is associated with adverse outcomes, including mortality.

It is also notable that slower nonculprit artery flow was associated with the presence of regional wall motion abnormalities in the distribution of the nonculprit artery. Indeed, Kramer *et al.* (16) have shown that five days after an acute first MI in patients with single-vessel disease, there is reduced circumferential shortening in remote noninfarcted regions. It has been speculated that this may be due to either

reduced coronary vasodilation in remote territories (17), the mechanical tethering of the remote region to the infarcted region or changes in regional mechanical loads (16).

There was also concordance in culprit and nonculprit territories in the development of systolic flow reversal, or the no-reflow phenomenon. Recent Doppler velocity wire data suggest that systolic retrograde flow reversal is more frequently observed in the presence of the no-reflow phenomenon (17,18). The visual appreciation of grossly pulsatile flow may be the angiographic analogue of these more refined Doppler wire observations (17,18). Previous animal laboratory studies have shown that focal areas of necrosis

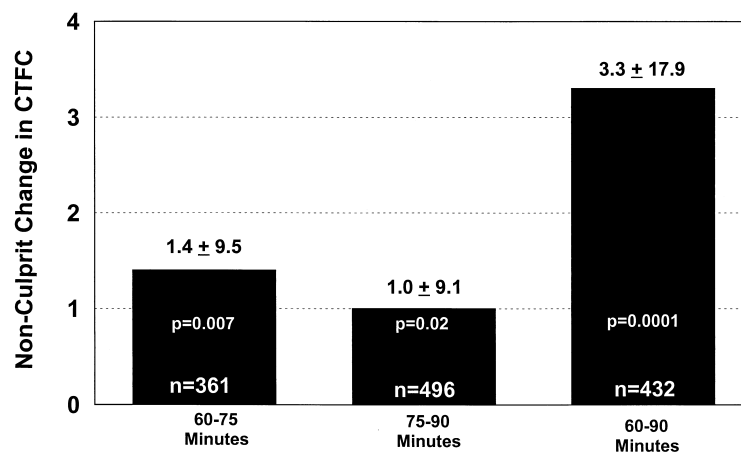


Figure 4. Paired analysis of the change in the nonculprit artery CTFC over time. Flow improved by 1.4 frames between 60 and 75 min ($p = 0.007$, median = 1), by 1.0 frame between 75 and 90 min ($p = 0.02$, median = 0.59) and by a total of 3.3 frames between 60 and 90 min after thrombolytic administration ($p = 0.0001$, median = 2).

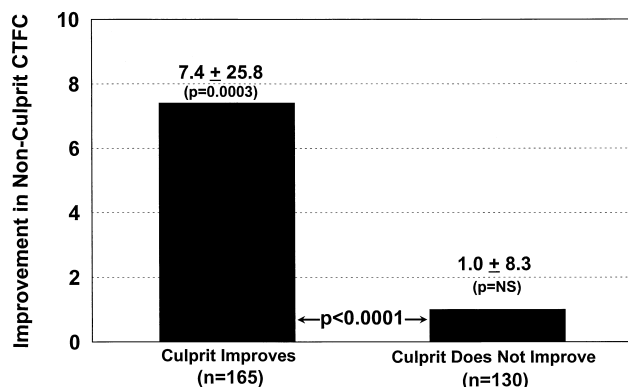


Figure 5. Relationship between improved nonculprit artery flow and improved culprit artery flow between 60 and 90 min after thrombolytic administration. When flow improved in the culprit artery, flow in the associated nonculprit artery improved by 7.4 frames ($p = 0.0003$), but when flow in the culprit artery did not improve, there was no significant improvement in nonculprit artery flow (1.0 frame, $p = \text{NS}$).

(micro-infarcts) occur in the nonoccluded (remote) posterior segments of the left and right ventricles after occlusion of the proximal LAD in dogs (19–23). It may be speculated that delayed nonculprit artery flow may be the result of more extensive necrosis in shared microvasculature, or occur as a consequence of vasoconstriction, perhaps mediated by local neurohumoral reflexes. Although we studied nonculprit

arteries that did not appear to lie in the direct distribution of the culprit artery, these abnormalities in wall motion and systolic flow reversal suggest that there may be shared territories of injury.

Aside from protocol-mandated nitrate administration, this study did not control for drug effect, and it is possible that other drugs (e.g., beta blockers, calcium channel blockers, adenosine, sedatives) may have also modulated coronary flow globally. Gregorini *et al.* have shown that PTCA and stenting improve nonculprit artery flow from 53 to 42 frames (24), and stenting improves nonculprit flow from 40 to 25 frames (25). Infusion of the beta-adrenergic blocker phentolamine further improved the nonculprit artery CTFC to 19 frames and improved fractional shortening in nonculprit territories (24,25). We have also reported that in the setting of acute coronary syndromes, PTCA accelerates flow in the nonculprit artery in the RESTORE study (26). Thus, neural mechanisms may be responsible in part for simultaneous inhibition of flow and left ventricular function in remote regions.

Hemodynamic perturbations in the setting of acute MI explain some, but do not appear to explain all, of the flow delays in nonculprit arteries. The flow in patients with and without acute MI were compared in a multivariable model that included both acute MI and normal patients' hemodynamic data. Even when adjustments were made for the hemodynamic abnormalities, nonculprit arteries in the acute

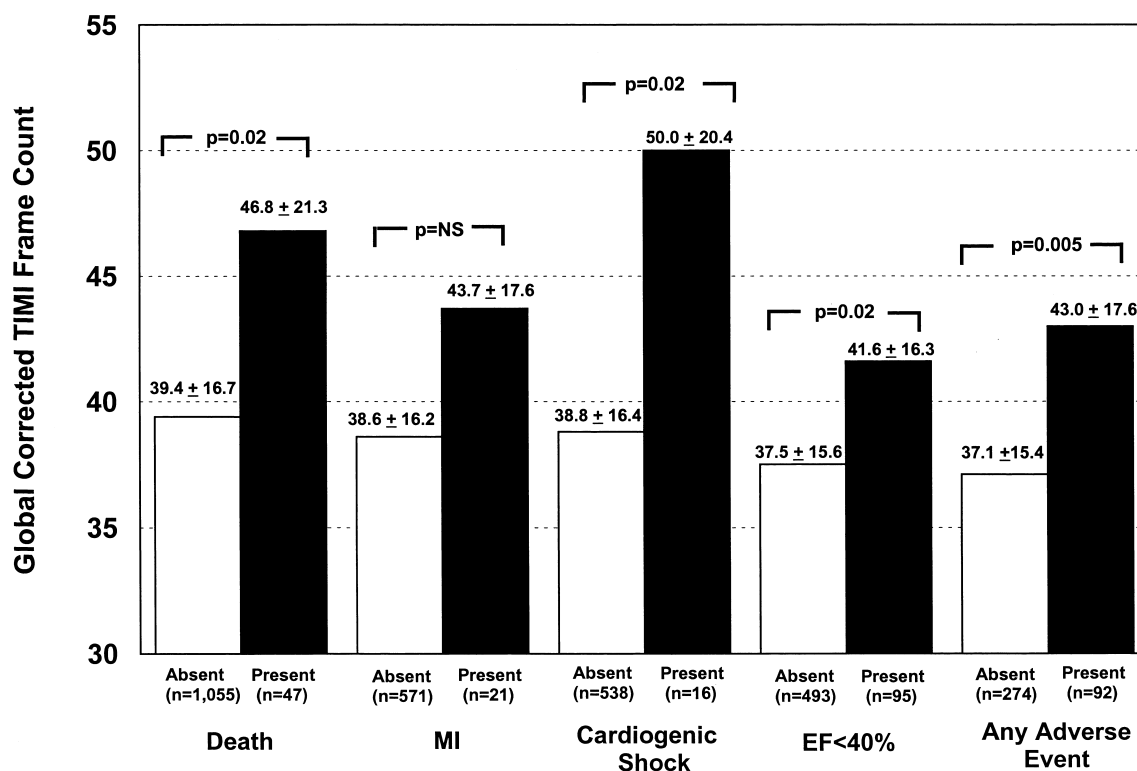


Figure 6. Relationship between the global CTFC (the average CTFC in all three arteries) and adverse outcomes. Patients who sustained adverse events had lower global frame counts.

MI setting were still slower than normal arteries in the absence of MI by almost 11 frames, or nearly 50%.

In a recent article by French et al. (27), nonculprit artery flow in the setting of acute MI (HERO-1 trial) was slowed to 24 frames 90 min after thrombolytic administration (median 20.9), lower than the 30.9 observed in this analysis. Part of the reason for this difference may be due to the fact that the French analysis only included patients with angiograms at both 90 min and 48 h (251 of 412 patients), resulting in a potential selection bias towards patients without an adverse event. It can be hypothesized that these patients had better flow, as we demonstrated in this article, and thus skewed the nonculprit CTFC lower. The HERO study also used different antithrombotic agents and the distribution of the infarct-related arteries may have also been different (27).

Study limitations. The nonculprit artery CTFC could not be ascertained in 6.4% of consecutive patients in the TIMI 10A, 10B and 14 trials ($n = 108/1,697$ of patients with an open nonculprit artery), and the culprit artery CTFC could not be ascertained in 2.2% ($n = 30/1,341$) of patients with an open culprit artery. Hemodynamic data from the TIMI 4, 10A and 10B trials were not available, and the assessment of the underlying effects of hemodynamic variables on nonculprit arterial flow was conducted using data from the TIMI 14 trial alone. Wall motion was assessed qualitatively, and in most instances a single-plane projection (the right anterior oblique) was used.

Recently, we demonstrated that when the force of injection is varied between the 10th and 90th percentile for injection rates, the CTFC may change by approximately two frames (28). Other groups have recently reported that the TIMI Frame Counting method is very reproducible, with a coefficient of correlation of >0.97 between observers, and differences between observers of <0.75 frames in the study of French et al. (29,30). While the CTFC is a measure of time, it does not account for vessel length or volume, and it is therefore only an index of coronary flow and velocity. More direct measurements of flow and velocity using other methods, such as PET scanning, Doppler wires or magnetic resonance imaging (MRI), are needed to further verify these observations. Indeed, Doppler velocity wire studies and PET studies have both confirmed that coronary flow reserve is impaired in nonculprit arteries in the acute MI setting (31,32).

Given the multiple variables that were analyzed in this study, it is possible that some spurious results may have emerged. However, many of the p values in this study are below the 0.01 level, indicating that they are unlikely to be spurious, and many of the variables were validated in two random cohorts of patients (slower culprit artery CTFCs, TIMI grade 3 flow in the culprit artery, LAD culprit artery location, pulsatile flow, greater culprit artery reference diameter, the nonculprit artery minimum diameter and the double product), as was the multivariable model. Despite

the associations identified here, additional work is needed to further understand the causes of abnormal nonculprit flow on a more fundamental level. The association between impaired global flow and outcomes does not definitively prove that slower global flow causes adverse outcomes. It is possible that slower global flow may be a marker for impaired ventricular function or hemodynamic compromise. It is unclear if slower global flow is a cause of or a result of these associated ventricular function and hemodynamic abnormalities.

Conclusions. Flow in nonculprit arteries is slowed by 45% at 90 min after thrombolytic administration, and slower nonculprit artery flow is linked to slower culprit artery flow. Relief of the residual stenosis in the culprit artery restored flow that was equal to that observed in the nonculprit artery, but the resulting culprit artery flow was still slower than normal. Acute MI reduces flow globally, and slower global flow is associated with adverse clinical outcomes.

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